--CROSS-REFERENCE TO RELATED APPLICATIONS

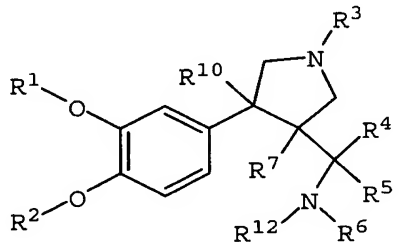
This application is a continuation of application Serial No. 09/731,591, filed December 7, 2000, now U.S. Patent No. 6,376,489, which claims the benefit of provisional application Serial No. 60/171,023, filed December 23, 1999.--

IN THE CLAIMS:

Cancel claims 1-45.

Add new claims 46-51:

--46. A method of inhibiting IL-1β release by monocytes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylO-aryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkylene$C(=O)R^7$, $C(=O)$-$C(=O)NR^8R^9$, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkylene$C(=O)OR^7$, $C(=O)C_{1-3}$alkylene$C(=O)OR^7$, C_{1-3}alkylene-heteroaryl, $C(=O)C(=O)OR^7$, $C(=O)C_{1-3}$alkylene$C(=O)OR^7$, $C(=O)C_{1-3}$alkylene$NH(C=O)OR^7$, $C(=O)C_{1-3}$alkyleneNH_2, and $NHC(=O)OR^7$;

R^4 is hydrogen, lower alkyl, haloalkyl, cyclo-alkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a hetero-cycle, aralkyl, and aryl, and R^7 can be optionally substi-tuted with one or more of RO^8, NR^8R^9, or SR^8;

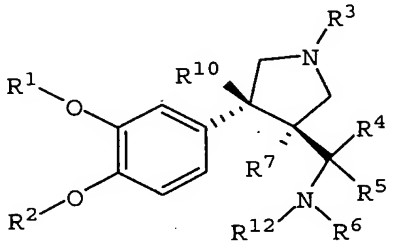
R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cyclo-alkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, hetero-alkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)$alkyl, $C(=O)$cycloalkyl, $C(=O)$aryl, $C(=O)$-Oalkyl, $C(=O)O$cycloalkyl, $C(=O)$aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

47. The method of claim 46 wherein the compound has the structure:



48. The method of claim 46 wherein the compound is selected from the group consisting of

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[benzylamino]methyl]}pyrrolidine carboxylate

Methyl (4S,3R)-3-(aminomethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[methylsulfonyl)amino]methyo}pyrrolidinecarboxylate

Methyl (4S,3R)-3-[(acetylamino)methyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(phenylcarbonylamino)methyl]pyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[phenylsulfonyl)amino]methyl}pyrrolidinecarboxylate

Bis{[(4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-carboxymethylpyrrolidin-3-yl]methyl}amine

1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

1-{(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

3-(S)-(1-Acetylaminoethyl)-4-(S)-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsulfonyl)-amine

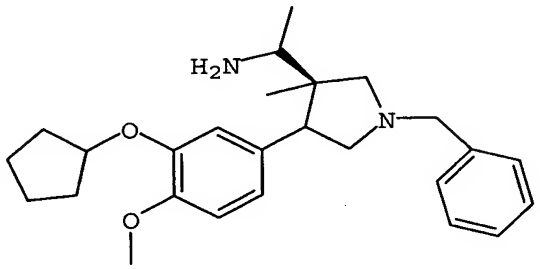
{1-[(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsufonyl)amine

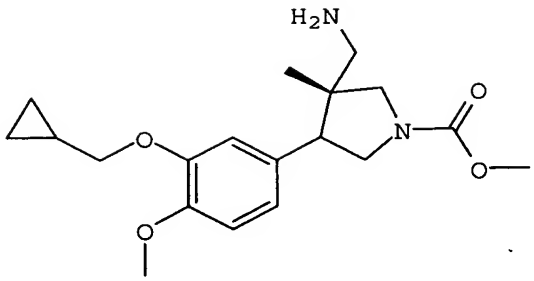
{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine

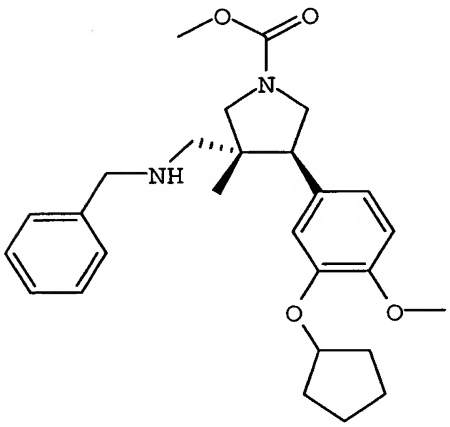
{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine, and

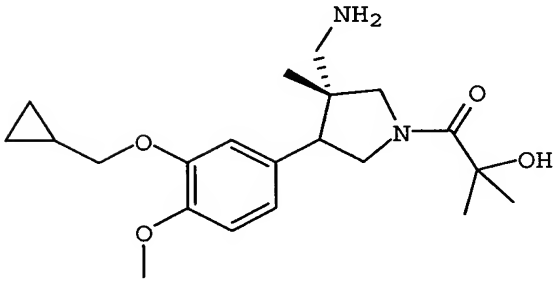
Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(methylamino)ethylpyrrolidine carboxylate.

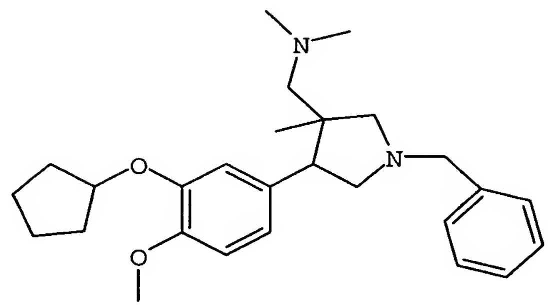
49. The method of claim 46 wherein the compound is the group consisting of:











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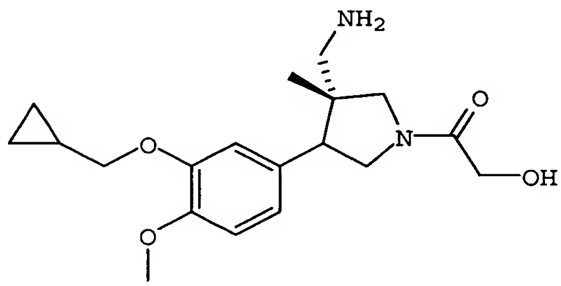
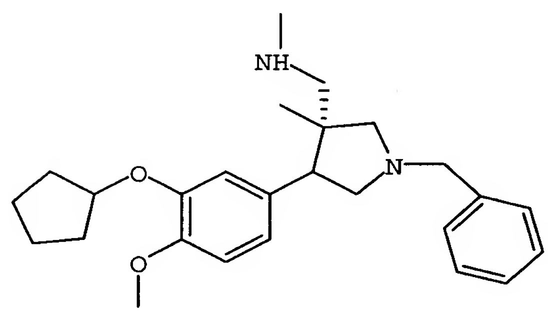
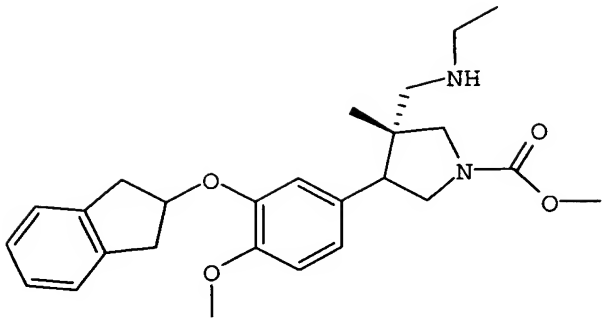
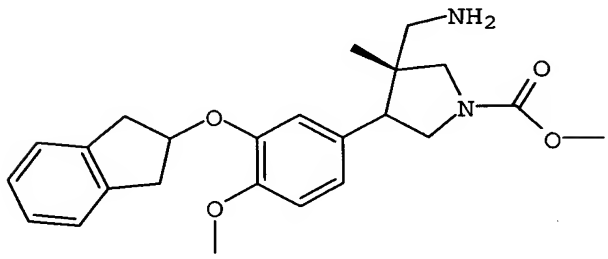


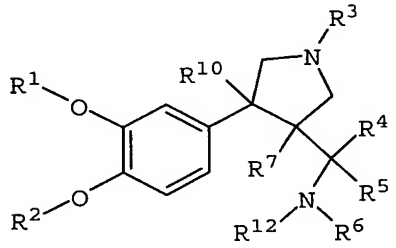




and



50. A method of inhibiting activation of human T-lymphocytes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearyl-Oaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneNH(C=O)OR^7, $C(=O)C_{1-3}$alkyleneNH_2, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, hetero-

alkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

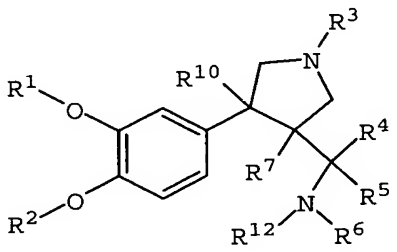
R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

51. A pharmaceutical composition comprising

(a) a compound having a formula



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylOaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of C(=O)OR^7, C(=O)R^7, C(=NH)NR^8R^9, C(=O)NR^8R^9, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl,

C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneNH(C=O)OR^7, C(=O)C_{1-3}alkyleneNH_2, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or C(=O)R^7;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, heteroalkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9,

and salts and solvates thereof;

(b) a pharmaceutically acceptable carrier; and

(c) a second therapeutic agent having utility in the treatment of rheumatoid arthritis.--